region **114** of the sifter is greater than the pore density of a central region **112** of the sifter. The pore density can smoothly increase from center to edge (e.g., as shown on FIG. **1***a*), or discrete central and peripheral regions can be formed, where the pore density is constant in each region. In cases where the central and peripheral regions are discrete, any number of intermediate regions can be included between the central and peripheral regions. Optionally, anti-fouling layers can be disposed at the substrate surface **118** and/or magnet surface **120** of the magnetic sifter.

[0021] In operation, an external magnetic field **106** is provided by a magnetic source **116**. Magnetic source **116** can be a permanent magnet, or it can be an electromagnet. Application of external magnetic field **106** to the sifter causes magnetization in layer **104**, which tends to provide high magnetic fields and field gradients at the sifter pores. These conditions are suitable for capturing magnetically tagged or labeled cells at the sifter pores. In this description, the terms "tagged" and "labeled" are used interchangeably to refer to cells having an attached magnetic marker. As described in greater detail below, altering external magnetic field **106** can provide controlled capture and/or release of magnetically labeled cells from the sifter pores.

[0022] The purpose of having a greater pore density at the periphery of the sifter than at the center is to provide improved flow rate uniformity through the sifter. FIGS. **2***a-b* show an example. FIG. **2***a* shows a typical flow rate distribution **204** in a channel **202**. The flow rate is greatest at the center of the channel and decreases towards the edges of the channel as a result of fluid viscosity. The side view of FIG. **2***b* shows such a channel after addition of a magnetic sifter **208** having greater pore density at the sifter periphery than at the sifter center (e.g., as shown on FIG. **1***a*). The pore arrangement of sifter **208** is preferably selected such that the flow rate distribution **206** is substantially uniform across the channel, as shown.

[0023] By having a greater pore density at the sifter periphery than at the sifter center, greater resistance is provided to fluid flow at the center of the channel than at the edge of the channel. This effect can be tailored to compensate for the flow rate distribution in an empty channel (e.g., as shown on FIG. **2***a*), thereby providing the desired flow rate uniformity. Detailed design of sifter hole patterns in accordance with these principles depends on details of channel/flow cell geometry and on the properties of the fluid being employed, especially its viscosity. Providing such detailed designs in accordance with these principles is within the skill of an art worker.

[0024] Practice of the invention does not depend critically on the geometrical details of FIG. **1***a*. Any pore arrangement having a greater pore density at the periphery of the arrangement than at the center of the arrangement can be employed. FIG. **3** shows an example of a circular arrangement, where the pore density is a smoothly increasing function of radius. Here, one of the pores is referenced as **302**.

[0025] Practice of the invention also does not depend critically on the shape of the sifter pores. Several possible pore shapes are shown on FIG. **4**. These examples include circular pores (**402**), bow-tie pores (**404**), square pores (**406**), rectangular pores (**408**), and notched rectangle pores. (**410**). For the bow-tie and notched rectangle pores, there are focus points (e.g., **412***a*, **412***b* and **414**) which tend to be preferential sites for cell capture. The focus points can have flat tips (as shown) or sharp tips. Pore sizes can range from less than one micrometer wide to about 100 micrometers wide. For applications in cell separation, the slit width can be chosen to be slightly larger than the average diameter of cells in a mixture, and the slits may be square in shape.

[0026] In a preferred embodiment, a magnetic sifter as described above is included in a flow cell that includes an optical window in proximity to the pores of the sifter. FIG. **5** shows an example in exploded view. A magnetic sifter **506** including pores (i.e. through holes) **508** is clamped between O-rings **510** by flow cell members **502** and **504** which provide a fluid connection (dashed lines) between channels **512** and **514** that passes through magnetic sifter **506**. An optical instrument **520** is disposed such that light from the pores of the sifter can reach instrument **520**. In this example, flow cell member **502** is fabricated from a clear material (e.g., transparent plastic), and can serve as the optical window. Alternatively, a transparent window (not shown) can be included in an otherwise opaque flow cell member **502** to provide optical access to captured cells.

[0027] This embodiment can be interfaced with a fluidic system, and can be employed to capture and release cells, including circulating tumor cells, stem cells, hematopoietic progenitor cells, cardiac progenitor cells, etc. Flushing with a buffer or cell culture media solution can be employed in connection with this embodiment to harvest the captured cells for subsequent analysis or cell culturing.

[0028] Embodiments of the invention are suitable for sequential processing of biological cells. FIG. **6** shows a simple example, where a channel **602** includes a first magnetic sifter **604** and a second magnetic sifter **606**. The operation of first sifter can provide a processed cell stream **608** between first sifter **604** and second sifter **606**. This processed cell stream can then serve as an input to the second sifter **606**. Any number of sifters can be cascaded in this manner. The magnetic tags used for the several sifters in such an arrangement can be the same or they can be different.

[0029] Stacking of sifters also enables multiplex magnetic separation. For example, to perform a two-plex separation, two sifters can placed in series as shown on FIG. **6**. A cell suspension can be mixed with two magnetic particles with distinctly different properties (e.g., magnetic saturation fields, saturation magnetizations, and/or particle sizes) and distinctly different targeting/capture antibodies specific to two different cell types. To illustrate two-plex separation, we consider labeling cell suspensions with two particles with different saturation fields, referred to as particle A (low saturation field) and particle B (high saturation field). For an arbitrary magnetic sifter design, particle A will be easier to capture, due to a lower saturation field, while particle B will be more difficult to capture. The two sifters can be designed such that the first sifter **604** generates on average a weaker magnetic field gradient in the pore than the second sifter **606**. The average field gradient across a sifter pore can be tuned by varying the applied external field strength, pore width, sifter magnetic film thickness, and/or the saturation magnetization of the sifter film. Since the average field gradient of a pore depends linearly with the saturation magnetization of the film, sifter films with variable alloy compositions could be an elegant approach to tuning the average gradients.

[0030] In this scheme, cells labeled with particle A, the easier of the two particles to capture, are captured by the first sifter **604** with weak magnetic field gradients. Cells labeled with particle B pass through the first sifter uncaptured and are included in processed cell stream **608**. The cells labeled with